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BOSTON UNIVERSITY

GRADUATE SCHOOL

Thesis

MODERN CONCEPTION OF THE FUNCTION OF THE THYROID GLAND

(From a Comparative View Point)

Submitted by

Giovannina Culosi

(S.B. Boston University, 1926)

In partial fulfilment of requirements for

the degree of Master of Arts

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MODERN CONCEPTIONS OF THE FUNCTION OF THE THYROID GLAND

(From a Comparative View Point)

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MODERN CONCEPTIONS OF THE FUNCTION OF THE THYROID GLAND

(From a Comparative View Point)

I. COMPARATIVE ANATOMY

1. Amphioxus and Ammocoetes

In Amphioxus and Ammocoetes the thyroid is a sausage shaped glandular organ which branches in a forklike manner and retains its opening in the pharynx. It is lined with ciliated epithelium and secretes mucus. In Petromyzon the connection with the pharynx is broken, and the gland consists of a number of closed vesicles lined by tall columnar epithelium which secretes a colloid substance.

2. Elasmobranchs

In Elasmobranchs the thyroid is a large yellowish white organ situated at the anterior end of the ventral aorta, in front of the bifurcation of the branchial artery. In some species the anterior end is elongated and ends into a point. In other species the gland is situated on the coraco-hyoid muscles, just under the coracomandibular, and may be flat, spheroidal or irregular in shape. Throughout the Elasmobranchs the shape of the cells lining the vesicles varies in different species; in some cases it is tall columnar epithelium, in others low cuboidal. The secretion consists of a colloid substance similar to that of other vertebrates.

No parathyroids have been described in Elasmobranchs.

3. Teleostei

In Teleostean fishes the gland is unpaired, lies beneath the copulae of the branchial arches, and surrounds the anterior end of the branchial artery. It consists of loose connective tissue which does not form a definite membrane around the gland but covers it and the surrounding vessels. The vesicles are scattered throughout the connective tissue and seem to be arranged in rows. The walls of the vesicles consist of a single layer of columnar epithelium resting on a basement membrane which is formed by the surrounding connective tissue. The thyroid of Teleostean fishes is of interest due to the fact that goiter is common among them and is even said to become carcinomatous (Marine, Lenhart, and Gudernatsch).

No parathyroids have been described in these fishes.

4. Urodela

In Urodela the thyroid occupies a more superficial position than in the Anura. In Sperlerpes ruber, where the vesicles are of the same size as those in the frog, the gland is more vascular, there is less connective tissue than in the frog, and the vesicles are more closely packed together. The colloid substance is the same as that of other vertebrates.

5. Anura

In Anura - the frog - for example, the gland consists of

a number of closed vesicles the walls of which are lined by a single layer of cuboidal epithelial cells. The intervesicular tissue is not of a cellular nature as in mammals but consists of fibrous connective tissue in which are embedded many nuclei and blood-vessels.

In this case there are accessory thyroids which have the same structure as the main thyroid.

Parathyroids are described by Ecker.

6. Reptiles

In some families Ophidia and Chelonia, the gland is unpaired, while in Lacertilia it is bilobed in the early stage but paired in the adult.

Parathyroids are present.

7. Aves

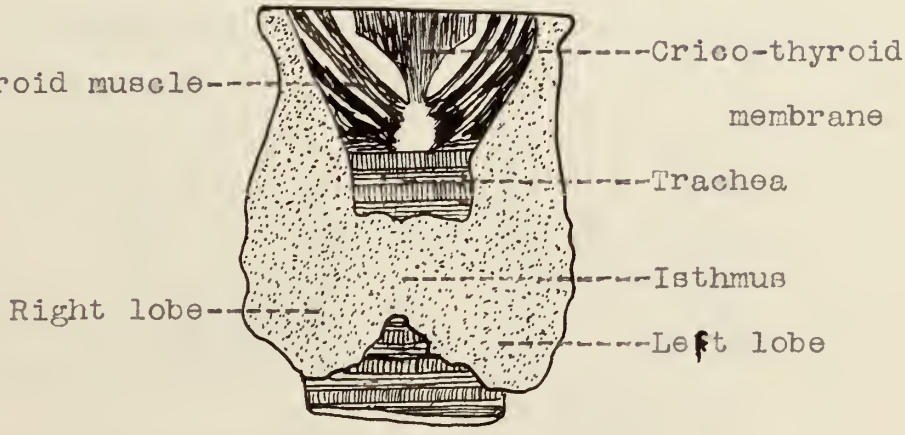
In birds the general features of the gland are the same as in Reptiles. The adult gland is a paired structure. The vesicles are usually small, and irregular in outline. There is a large amount of intervesicular tissue which in some species forms large areas of solid tissue.

The parathyroids of birds contain much fat, but do not contain vesicles like those of the reptilian gland which cannot be distinguished from parathyroid.

8. Mammals

a). General

The thyroid gland is a vascular organ situated at the sides and front of the neck*. It consists of a right and left lobe connected together by an isthmus.



* View of Thyroid Body (Man)

(After Morris Human Anatomy)

****

b). Man

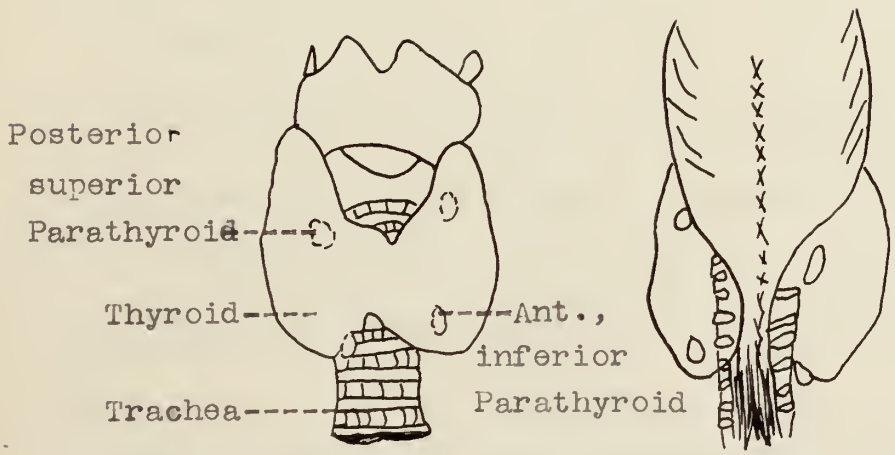
In man the gland is also a vascular structure, it consists

* Text-book of Physiology by Brubaker Page 522

of a right and left lobe connected together by an isthmus.

According to most observers there are four parathyroids, two on each side of the median line of the body. These may be either oval or pyriform in shape and may be connected by a stalk, in which run the parathyroid vesselt to the thyroid gland.

The posterior superior parathyroid is more constant in position than the anterior inferior. It usually lies on the posterior wall of the oesophagus at the level of the lower edge of the cricoid cartilage, internal to the lower margin of the lateral thyroid lobe.



A = Front view; B = Posterior view.

* Diagrams showing relations of thyroid, parathyroid, and trachea, in human subjects.

****

* Internal Secretion and the Ductless Glands by Vincent Page 285.

The anterior inferior parathyroids are very inconstant in position and relation; sometimes they are found as low down as the level of the tenth tracheal ring. The position and relation of these is very important in surgical treatment of thyroid disorders.

c). Monkey

Vincent, while working in conjunction with Professor W. A. Jolly, found that in monkey the thyroid lobes are sometimes united by an isthmus and sometimes are not.

d). Dog

The thyroid of the dog usually consists of two distinct lobes not connected by an isthmus. According to Ellenberger and Baum, the thyroid consists of two lobes connected by an isthmus. In small dogs the isthmus is absent, while in larger dogs it is present.

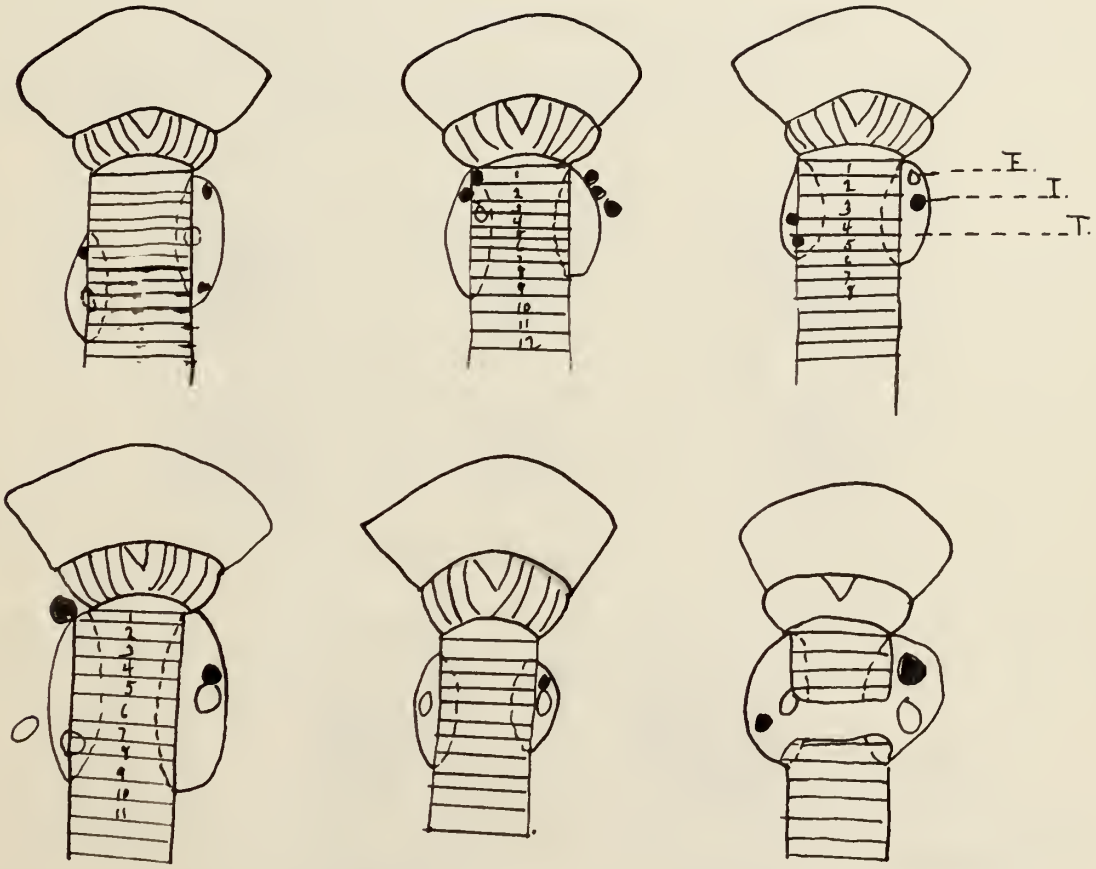
Usually there are four parathyroids, some are internal and some external, but there are as many as five, and sometimes it is impossible to see more than three. (See diagram p,7).

e). Cat

In the cat the two lobes are not usually connected. There are four parathyroids, two internal and two external. (See p,8).

f). Rabbit

In the rabbit there are usually four parathyroids. The external parathyroids are situated at a considerable distance from the thyroid lobe. This accounts for the fact that in the earlier extirpation experiments they were always left behind.



E = External parathyroid; I = Internal parathyroid; T = Thyroid.

* Diagrams showing positions and relations of thyroid, parathyroid and trachea in the dog.

* Internal Secretion and the Ductless Glands by Vincent Page 287

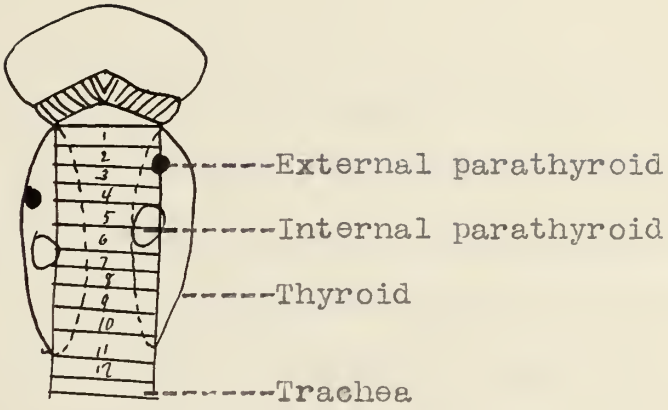
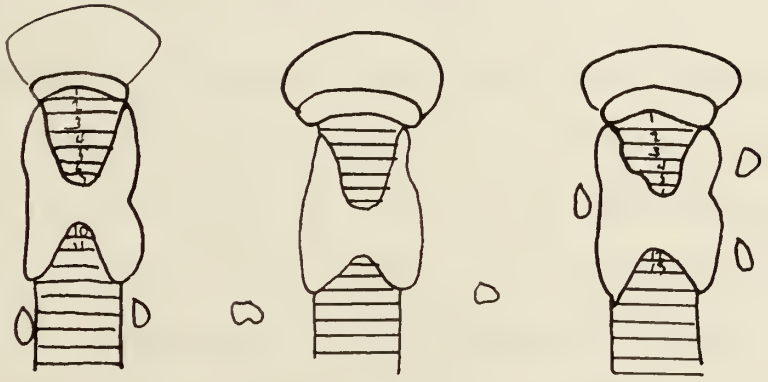
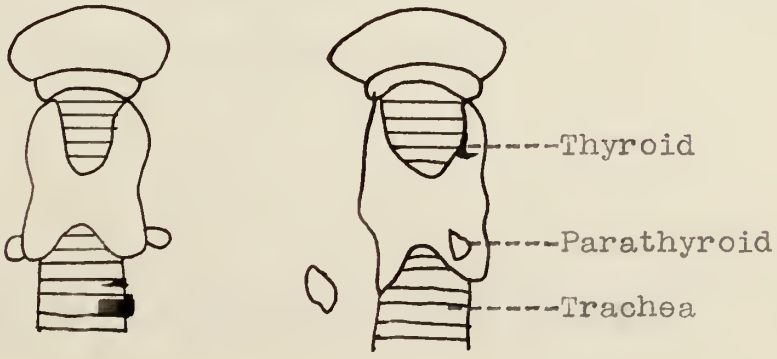


Diagram showing relation of thyroid, parathyroid and trachea in the cat. (From Vincent page 287).





Diagrams showing relation of thyroid, parathyroid (internal and external), and trachea, in rabbits. (From Vincent page 288).

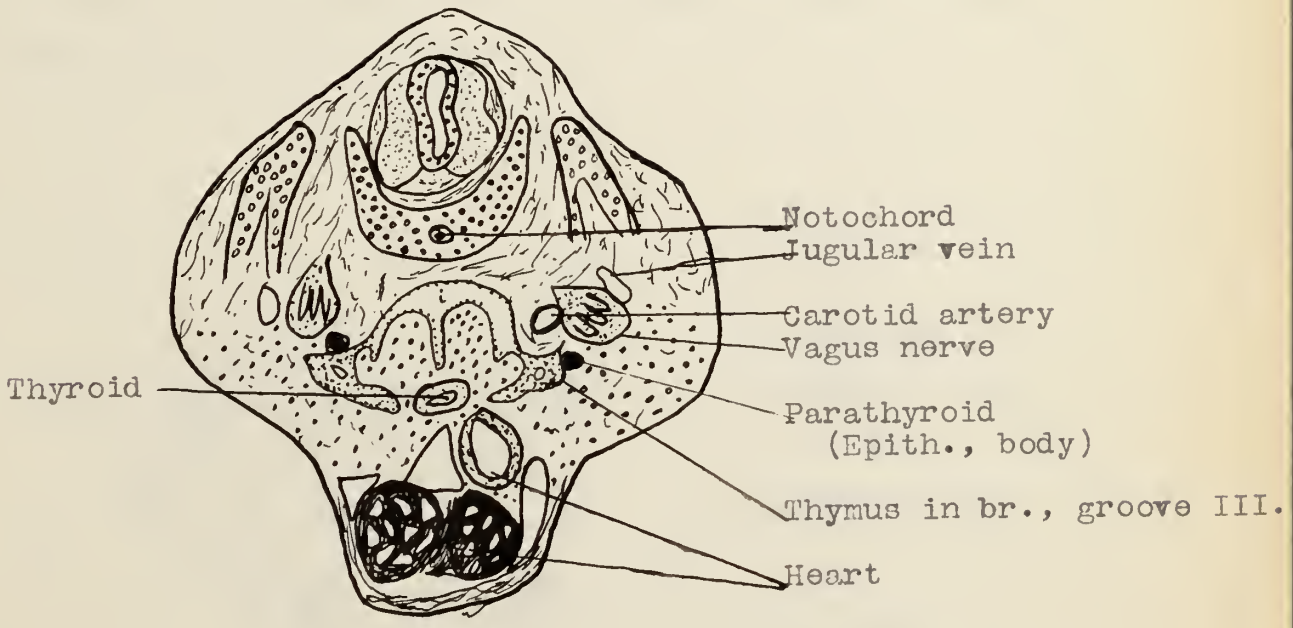
II. ANCESTRY

Owing to the survival of one class of vertebrates namely the Cyclostomes it has been possible to establish the origin of the thyroid of all higher vertebrates as a direct metamorphosis of the endostyle organ. * " The endostyle organ is an elaborate ventral mid-line pharyngeal gland in tunicates, amphioxus, and ammocoetes." In tunicates and amphioxus it opens into the pharynx by means of a groove. In ammocoetes the opening into the pharynx is reduced to a large duct. During the metamorphosis of ammocoetes the endostyle organ undergoes atrophy with complete loss of three of its specialized types of epithelium including the duct, and thus the ductless thyroid follicles of the adult are formed from one persisting type of endostyle epithelium. The ductless thyroid follicles in cyclostomes arise only from the endostyle organ. Studies in the embryology of the thyroid of fishes, amphibians, reptiles, and birds have shown that it arises from a median single ventral tubular downgrowth of the pharyngeal endoderm slightly anterior to the first aortic arch.

* Physiological Reviews, Vol., II., 1922. Page 521.

III. EMBRYOLOGY

* The thyroid gland arises as an evagination from the epithelium of the pharynx. It first appears in embryos of 3-5mm., in length, as a ventral outgrowth of the epithelium of the floor of the pharynx, at the point where the tuberculum impar and the two paired anlagen of the tongue join.



Transverse section through the region of the third branchial groove of an Echidna embryo. Mauer.

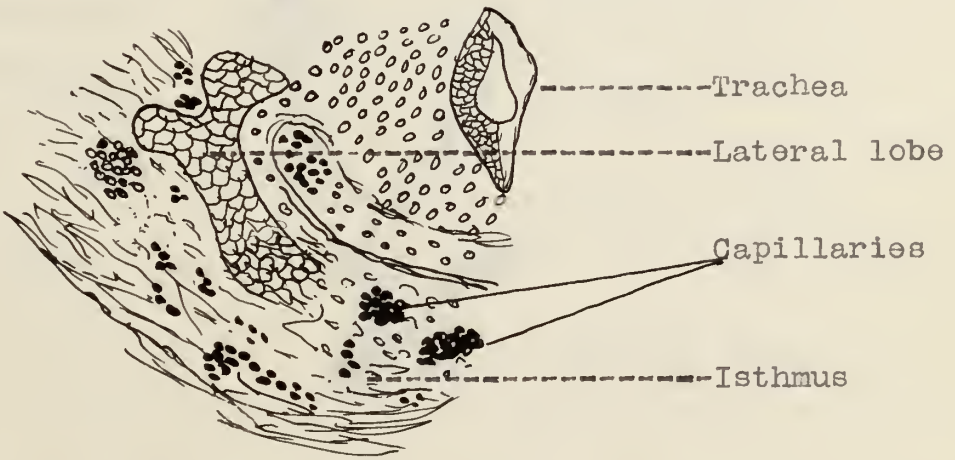
i = pharynx, below which are the paired anlagen of the tongue.

From Bailey-Miller Embryology page 333.

****

* This statement comes from Bailey-Miller Text-book of Embryology page 332, the author does not state kind of embryos.

The evagination grows into the mesodermal tissue in the ventral wall of the neck, and forms a transverse mass of epithelium. The epithelium breaks up into cords of cells, these by a process of budding grow caudally along the ventral surface of the larynx. At first the cells are surrounded by connective tissue, but later they become surrounded by a network of capillaries. (See diagram). Finally these cells break up into small masses which become hollow and form alveoli. Secretion of colloid begins toward the end of foetal life or soon after birth.



* Section of the right half of the thyroid gland of a pig embryo 22.5 mm., Born.

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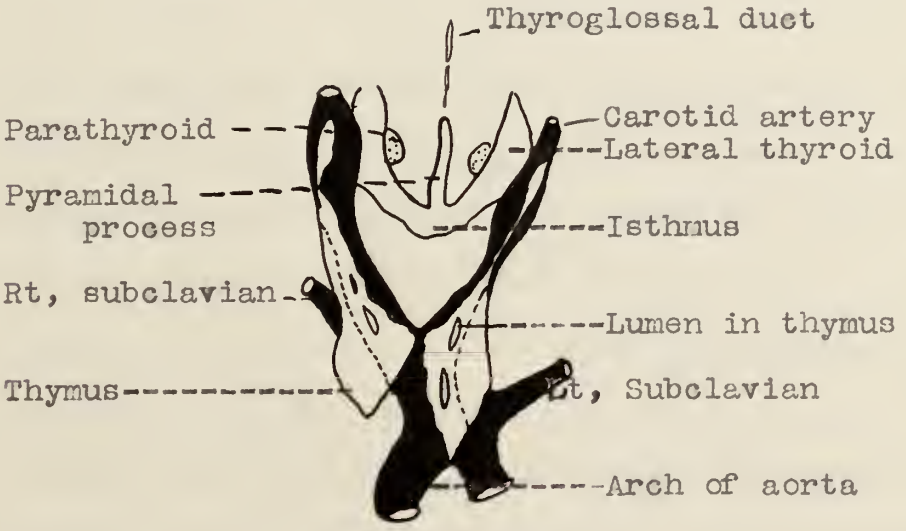
*Text-book of Embryology by F. R. Bailey and M. Miller Page 334.

As the embryo grows the gland also grows until it reaches its final position. As it grows toward its final position it enlarges laterally and forms two lobes; these two lobes remain connected by a structure known as the isthmus. The pyramidal process is believed to be either a secondary outgrowth from the isthmus or one of the lobes, or a remnant of the thyroglossal duct.



* Diagram showing relation of thyroid, parathyroid and thymus.

****

* Text-book of Embryology by F.R. Bailey and M. Miller Page 334.

IV. HISTOLOGY

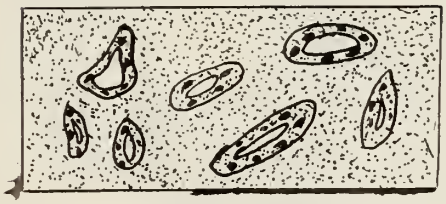
1. Gross Structure

The normal human thyroid weighs from 20-25 grams, and does not exceed 0.35 grams/kilo of body weight. Statistical data shows that the gland is slightly larger and heavier in the female than in the male. The gross outline of the gland varies. The greatest variation occurring in the isthmus or pyramidal process. In the normal gland the isthmus consists of a band of tissue from 1-2cm., in width, and from 1/2 - 1 cm., in thickness. It connects the two lateral lobes across the trachea anteriorly just below the level of the cricoid cartilage. The presence of a pyramidal process and a thyroglossal stalk is due to the incomplete absorption of this part of the thyroid which normally takes place between the fifth and eight week of foetal life. In severe endemic goiter districts, approximately 95% of human thyroids have a well formed pyramidal process, and the thyroglossal stalk is frequently continuous with the foramen caecum. Similar variations occur in animals, for example, in congenital goiter of dogs and sheep the thyroid lobes are usually joined by an isthmus while normally the isthmus (in these animals) is absorbed before birth.

2. Microscopic Structure

Morphologically the thyroid is one of the simplest tissue and resembles very closely lung tissue. (See diagram on next page).

It is one of the most labile tissues in the body capable of rapid overgrowth and of equally rapid involution. The gland has only



* Lung tissue (general appearance)

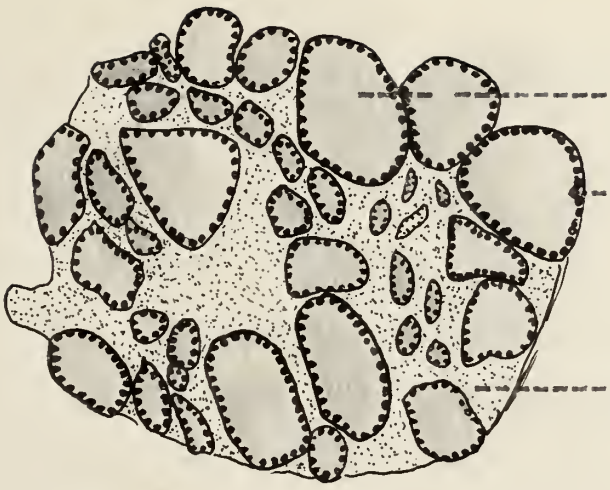
** Thyroid tissue (general appearance)

****

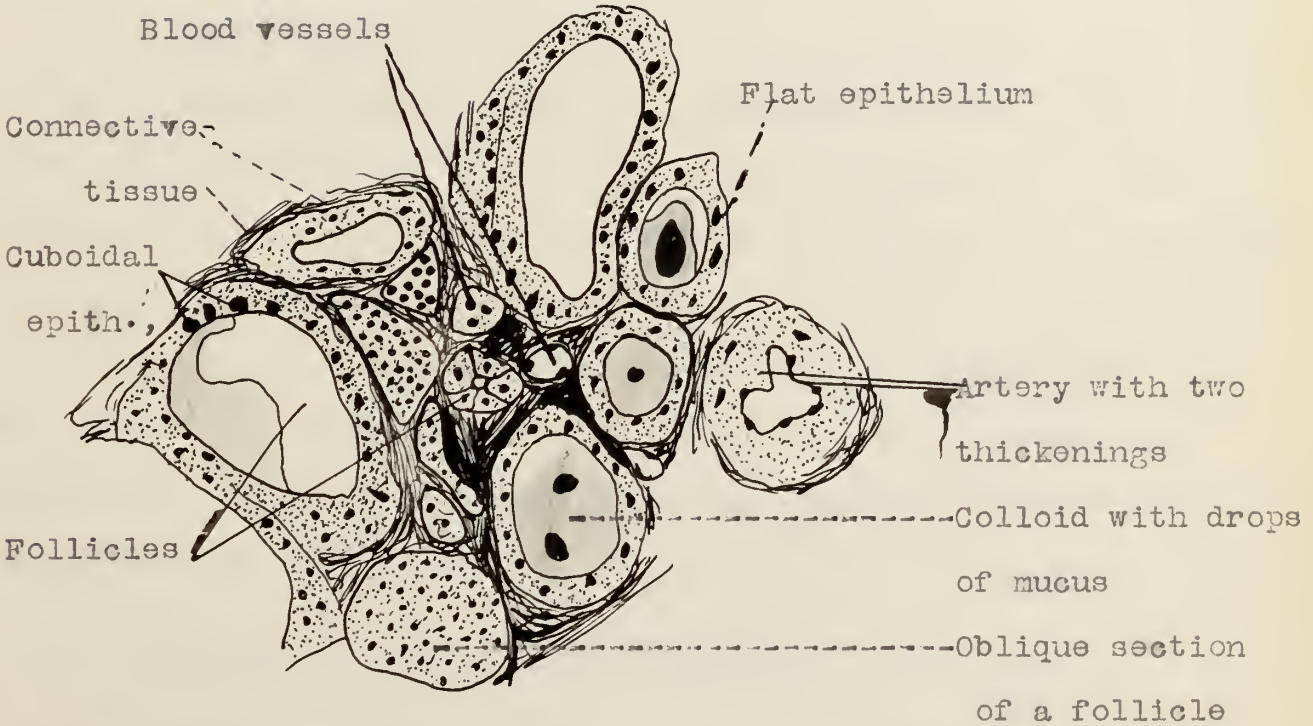
one cycle of cell changes and tends to repeat this cycle in response to all stimuli involving functional activity. By a glance at the above diagrams it is evident that thyroid tissue is distinguished from lung tissue by the presence of 'colloid' within the follicles of thyroid tissue. (See next page for microscopic structure.)

* Text-book of Histology by Lewis and Stöhr Page 305.

** " " " " " " " " " 227.



* Thyroid of Normal Dog.



** Section of a lobule of the Thyroid Gland of an adult man.

(x 220)

******

* Internal Secretion and the Ductless Glands by Vincent page 290.

** A Text-book of Histology by Stöhr page 227.

The gland is covered by a thin capsule of connective tissue which projects into the substance of the gland and thus divides it into masses of irregular form and size. The vesicles are separated from each other by connective tissue which is continuous from that which surrounds the entire gland. The vesicles of the gland of the adult animal are generally closed spherical sacs; but in some young animals (dogs) the vesicles are more or less tubular and branched, this appearance is supposed to be due to the method of growth of the gland and merely indicates that there is an increase in the number of vesicles.

Each vesicle is lined by a layer of epithelium which may be columnar, cuboidal or flat. Since there is no basement membrane the epithelial cells are in indirect contact with the connective tissue reticulum which supports the acini. The follicles vary in size and shape, sometimes they are round, sometimes they are elongated, and occasionally they branch or communicate with one another. The colloid material contains an iodine compound, iodothyrin, which is responsible for the chemical and physical properties of the gland.

a). Theories of Colloid Formation

According to Langendorf the follicles consist of two kinds of cells:-

(1). Chief cells

(2). Colloid cells

Langendorf believed that the chief cells in time change into colloid cells; while the colloid cells secrete a substance known as 'colloid.' During the formation process the cells become lower and their contents including their nuclei change into the colloid mass.

Hurthle distinguished two processes of colloid formation:-

(1). That in which the cells remain intact.

(2). That in which the cells become destroyed, and claims that the cells of Langendorf take part in the former process, while in the latter process they first become flattened and then change into the colloid substance.

The secretion in the cells is in the form of granules. This colloid material enters the lymph channels either directly by a rupture of the acini, or indirectly by a percolation of the substance into the intercellular clefts from where it is carried into the larger lymphatics. The internal secretion of the gland is known to contain a hormone which acts as a chemical stimulus to other tissues thus increasing their metabolism.

V. EARLY VIEWS CONCERNING THE FUNCTION OF THE THYROID

1. Galen

According to Galen the function of the gland (thyroid) was to secrete a fluid which served to moisten all parts of the larynx and passage of the throat.

2. Wharton

In 1656 Wharton gave a fairly good account of the thyroid. He described the gland as being more full of blood, viscid, and solid than any other gland. He attributed four functions to the gland:-

a). *"The first and principal use of the gland, according to Wharton was to take up superfluous moisture from the recurrent nerve and bring it back again into the vascular system by the lymph channel.

b). To cherish the cartilage to which it is fixed which is rather of a chilly nature by its own heat, for the gland is copiously supplied with arteries, and is very rich in blood so that it may continuosly impart heat to its neighboring parts.

c). To contribute by its exhalations to the lubrication of the larynx so as to render the voice more smooth, melodious, and sweet.

d). To contribute to the round contour of the neck, for it fills up the empty spaces about the larynx, and makes its protuberant parts almost smooth, especially in the female sex, to whom nature has given a larger gland, in order to render the neck more even and beautiful."

* Internal Secretion and the Ductless Glands by Vincent page 316.

3. Verheyen

Verheyen believed that the gland served to moisten its neighboring parts, and because it is very large, there is an apparent reason why it should have a very large duct or a very conspicuous one which has not yet been discovered.

4. Haller

Haller in his text-book written in 1776 discusses the anatomy of the gland and also the valueless attempt to find a duct. So that at this time the ductless gland such as the thyroid, thymus and spleen were classed together as glands without ducts, which secrete a special fluid which is taken up by the veins and distributed to the general circulation. This does not differ from the modern conception.

In 1834 Cruveilhier stated that the use of the thyroid secretion was unknown. At about this time Sir A. Arlisle supposed that the gland served as a protection to the delicate vocal organs, against the variation of the external air.

5. Morgagni

Morgagni is undecided as to whether the gland has a duct or not. He described vesicular cavities in enlarged glands, which he thought to be normal cavities which had been distended by the accumulation of secretion.

6. Santorini

Santorini fails to find a duct and thinks that the thyroid secretion is forced out by the contraction of the overlying muscles.

Although many theories existed concerning the secretion and elimination of the product from the vesicles into the circulation, yet the active function of the secretion was for a long time a subject of investigation, and the possibility of its being of any importance was scarcely suspected. In 1834 Cruveilhier as I have previously said, stated that the use of the thyroid secretion was not known. But ten years later, in 1844, Simon issued a theory concerning the function of the thyroid gland. Simon's theory briefly stated is that the thyroid exercises a secretory function on the blood supply to the brain.

At present it is believed that the function or *"physiologic action of the thyroid is to produce an internal secretion which after its entrance into the blood promotes favorably the metabolism of the neuro-muscular system at least. The myxedema and failure of mental powers are attributed to the loss or degeneration of the gland and hence its internal secretion, and cretinism to the arrest of its development."

VI. CHEMISTRY OF THE THYROID

Kendall is the first to give us a detailed account of thyroxin - the iodine compound - which occurs in the thyroid gland. According to Kendall all the chemical and physical properties of the gland are due to thyroxin.

* Text-book of Physiology by Brubaker Page 525.

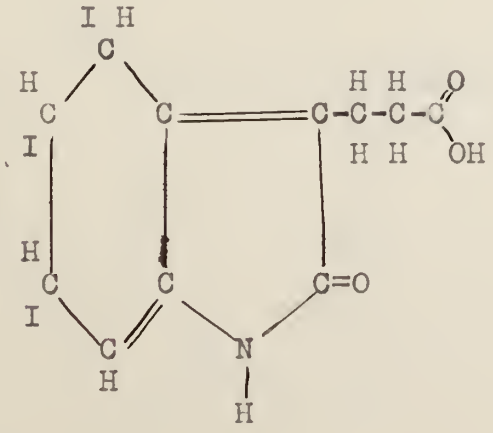
Thyroxin is a colorless, odorless, and tasteless crystalline substance. It is insoluble in aqueous solutions of all acids; soluble in sodium, ammonium, and potassium hydroxides; and slightly soulble in potassium carbonate. It is stable toward heat and has a melting point of about 250° C. Although it is a weak acid in the presence of mineral acids it posesses basic properties.

The iodine content of thyroxin is 65%, and of it's sulphate salt 60%. The molecular weight of thyroxin is about 585gms.

Thyroxin forms di-basic salts through the carboxyl and hydroxyl groups, in presence of alkali metals. In the presence of carbonates it forms monobasic salts with the carboxyl group alone. The imino group forms salts with mineral and formic acids but not with acetic. The salts of mineral acids are soluble in alcohol.

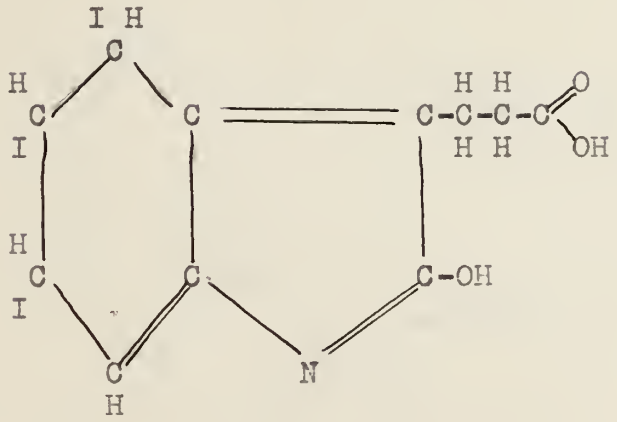
Thyroxin exists in four forms:-

1. The keto form having the imino carbonyl groups. This form has a melting point of 250° C.



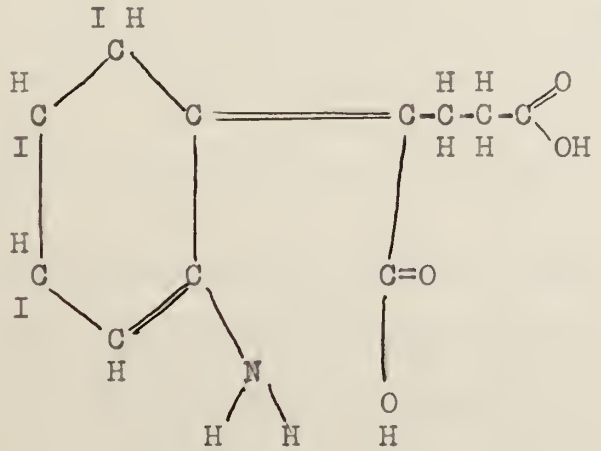
KETO FORM

2. The enol form in which the hydrogen has migrated from the imino to the carbonyl group thus forming the hydroxyl group. The melting point of this form is 204°C.



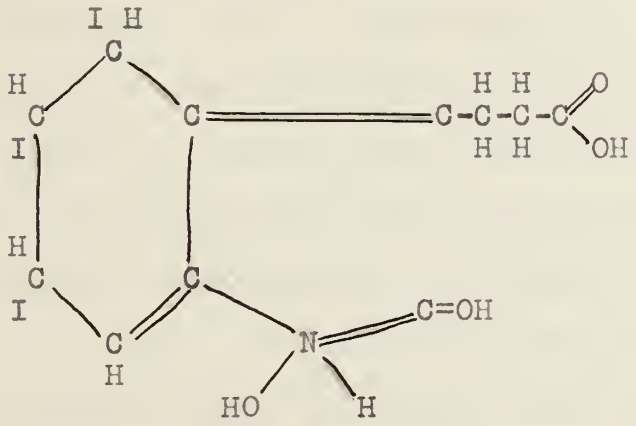
ENOL FORM

3. An open ring form in which the elements of water enter the molecule between the imino and carbonyl groups thus forming an open ring structure with the amino and carboxyl groups, which exist in salt formation, and is known as the amino carboxyl salt form. Its melting point is about 225° C.



OPEN RING FORM

4. A tautomeric form of the open ring form in which the elements of water add to the nitrogen thus forming the hydrate form which has a melting point of 216°C.



TAUTOMERIC FORM
of
OPEN RING FORM

VII. PHYSIOLOGICAL ACTION OF THYROID SECRETION

According to Kendall all the actions of the thyroid both physiologically and therapeutically are due to thyroxin. Experiments have shown that a single injection of thyroxin produces no fatal results, but that successive daily injections may bring about death.

1. Effects of Intravenous Injection

Intravenous injections of thyroid extracts produce a temporary fall of blood pressure. The fall is probaly due to a dilatation of the peripheral vessels throughout the body. That it is not due to vagus inhibition is proved by the fact that the fall is just as marked after administration of atropine as before.

2. Effects of Thyroid Feeding

Experiments by Gudernatsch and others show that by feeding tadpoles with thyroid substance the rate of metamorphosis is increased, as compared with controls. At first this reaction was supposed to be a test for thyroxin, but this is no longer so, since it has been found by experiments that the same results are produced by administration of iodides and iodized blood-serum. According to Kendall the action on metamorphosis (which is brought about with thyroxin) is not due to the organic nucleus, but to the iodine in the molecule which breaks off as Hypoiodous acid (HIO).

To determine the effect of thyroid feeding on gross weight most of the early experiments were performed on adult animals. Result - some experimenters reported an increase in the rate of growth, others a decrease, while still others no effect at all. Vincent reports Cameron as having repeated similar experiments except that he used young animals, and fed them with a dose of thyroid gland bearing a constant ratio to the body weight of the animal in question. * The results of Cameron's experiments are as follows:-

Continued small doses of dry gland administered to young white rats produced:

a). A definite and invariable decrease in the rate of growth.

* Summarized from Vincent's report.

Internal Secretion and the Ductless Glands by Vincent Page 333.

b). Hypertrophy of the organs concerned with increased metabolism, i, e, heart, liver, kidney, adrenals, etc., (confirmed by Hoskins and Herring).

c). Disappearance of fat (also confirmed by Hoskins and Herring).

d). The decrease in rate of growth was proportional to

(1). Amount of thyroid given.

(2). Iodine content in the gland given.

e). The hypertrophy varies with the dose and length of time during which it is administered and seems to be proportional to the amount of iodine contained in the dose given.

Experiments of thyroid feeding performed on human subjects give the following results. Feeding of large doses brings about a rapid pulse, nervous excitability, flushing of the skin, feeling of heat, and increased perspiration. In very extreme cases there are cervical sympathetic excitations such as dilatation of the pupil, retraction of the eyelid, physical excitement, sleeplessness, and tremors of the limbs.

3. Effects on Growth and Metabolism

The addition of a very small amount of thyroid to the food increases the nitrogenous metabolism as shown by the presence of an increased amount of nitrogen in the urine. This is accompanied by a corresponding increase in food consumption so that the difference in the growth curve of the thyroid fed animals and controls is very slight. Feeding larger doses of thyroid results in loss of weight due to the increased nitrogen elimination and loss of fat. There is also an increase in the amount of carbon dioxide given off, and

an increase in the basal metabolism.

The increase of basal metabolism is of clinical interest because it is characteristic of exophthalmic goiter which is believed to be accompanied by excessive thyroid secretion.

Thyroid feeding produces complete disappearance of glycogen from the liver even when the animals are kept on a diet rich in carbohydrate. No sugar appears in the urine, because the carbohydrates which are poured into the blood become oxidized in the tissues.

*Experiments show that when thyroid is administered to rats along with a diet deficient in vitamines growth is markedly retarded. Hoskins E.R. and Herring P.T., noticed a great enlargement of the heart, liver, kidney, pancreas, ovaries, testes, and suprarenals, in rats fed with thyroid. Theses observations were confirmed by Hewitt, who in addition found that there was a diminution in the size of the gland itself; and that on stopping the administration of the thyroid the organs returned to their normal size.

* From articles written by

Herring P.T. Quartly Jour, Exper. Physiol, Vol., II., 1917.
Hoskins E. R. & M.M., Endocrinology , " IV., 1920.
" M.M., " " VII.

4. Effect of Thyroid on the Heart

Intravenous injection of the whole gland produces a lowering of the blood-pressure; while injection of purified iodothyreoglobulin causes a slight lowering of the blood-pressure but the rate of heart beat increases after a latent period.

5. Relation of Thyroid to Immunity

Results of work done on this line are confusing and contradictory. In general it has been found that hemolysin and agglutinin formation are higher in thyroidectomized animals than in controls (rabbits), while antitoxin (diphtheria) formation is low in thyroidectomized animals (dogs, horses, and rabbits).

*Fjeldstadt working with thyroidectomized rabbits found no increase in agglutinin formation. Ecker and Goldblat found that the hemolytic litter of thyroidectomized animals (rabbits) was always higher than the controls. The reaction to infections as shown by a reduction in the amount of iodine stored and a tendency to hypertrophy and hyperplasia indicate that the thyroid is a very important indirect factor in resistance to infections.

VIII. EXTIRPATION EXPERIMENTS

Results produced by extirpation experiments vary (a) with the nature and completeness of the operation, (b) with the species

* Physiological Reviews Vol, II., 1922.

of animal, (c) with the age of the animal.

If the operation is complete, that is, if it includes removal of all the parathyroids along with the thyroid death will occur in some cases within a few days and in other cases within a few weeks. The most acute symptoms as result of complete parathyroidectomy are those shown by the carnivora such as dogs, cats, foxes, wolves and the young of herbivora. For the first two days there are no symptoms, except loss of appetite. * "There then supervenes marked exaltation of reflexes, which leads to the occurrence from time to time of fibrillar contractions of muscles and later cramp-like and clonic contractions, and eventually convulsive fits; these may be of considerable violence and alternate with intervals of depression. The body temperature may rise two or three degrees (centigrade) during the fit. The paroxyms are usually accompanied by rapid gasping respirations which may be synchronous with the heart beats; sometimes by vomiting and diarrhoea. Death may occur within a few days or the affection may last a long time and spontaneous recovery may occur. The syndrome is usually spoken off as 'tetany' (tetania parathyreopriva); which is in no way synonymous with 'tetanus'."

Tetany is due to the loss of parathyroid only, as shown by the fact that the symptoms appear only when the parathyroids are removed and can be cured by grafting parathyroids of an animal of the same species.

* An Introduction to the Study of the Endocrine Glands and Internal Secretion, by Schäfer E., Page 19.

In order to prevent tetany in operations for removal of thyroid tumours part of the parathyroid tissue is left in place.

Raynard was the first to perform extirpation experiments upon mammals. Result of the operation - in young animals death occurred within a few days. Post-mortem examination did not reveal the cause of death.

Astley Cooper removed the gland from two pups ten weeks old. Result - the animals recovered after a period of stupidity and malaise.

In 1856 Schiff performed the operation in various animals (rats, fowls, dogs, and cats) but obtained no definite reliable results. However, this did not discourage him and in 1884 repeated the same operation.- Result of the operation:-

1. Marked retardation of growth in young animals.

2. Ossification delayed. Growth of intermediate cartilage was interfered with, as shown by the fact that the long bones not only grew more slowly but where shorter than their normal adult length. The whole skeleton became involved, in general the animals remained smaller than the controls of the same litter.

3. The teeth were poorly developed.

4. The generative organs remained small and in some cases the ova and spermatozoa never matured.

5. The pituitary gland became enlarged and its anterior lobe contained vesicles filled with colloid.

6. In some cases the aorta became atheromatous.

7. Temperature fell below normal.

8. Abdomen became swollen.

9. The skin became thick and the hair coarse and stiff; but in some animals (goats) the hair became longer than in the normal animals.

10. Involution of the thymus was delayed and in some cases it did not occur at all.

11. Development of the central nervous system especially the brain was arrested.

In most of the young animals deprived of the thyroid there was a marked lack of intelligence, and were therefore described as cretins.

Biedl working with small dogs found no diminution of intelligence, although the head and face exhibited an infantile character as compared with controls. Eislsberg working with pigs obtained same results.

Results of thyroidectomy in adult animals:-

1. As result of thyroidectomy the animals became indolent.

2. Digestion was weak.

3. The animals became constipated.

4. The skin was dry, the hair coarse and lustreless, and easily fell off.

5. Eczema was common.

6. The number of erythrocytes in the blood was reduced, and the number of leucocytes increased.

7. Hypertrophy of the pituitary gland.

8. Metabolism of albumin was diminished while that of carbohydrate was increased.

9. Hypertrophy of the pancreas accompanied by an increase in the number of pancreatic islands of Langerhans.

10. Metabolism of salts was lowered. This has been proven by the fact that after thyroidectomy there is less excretion in the urine of calcium, phosphorus, and magnesia chlorides.

Experiments show that these symptoms do not appear if a small piece of thyroid is left in place. Authorities believe that one fourth of the gland is sufficient to produce enough hormone for the normal and healthy functioning of the organism. The fact that the thyroid secretes a very vital hormone which is poured into the blood-stream and is thus distributed to the different parts of the body is confirmed by the following:

If a part of the gland is grafted upon any internal organ such as the spleen or the intestine all the morbid symptoms of thyroidectomy become arrested.

Administration of fresh or dried thyroid extract also arrests the symptoms of thyroidectomy, for it increases the resisting power of the organism against infectious diseases to which it is subject.

Since one of the most important functions of the thyroid is the regulation of the calcium metabolism of the organism, it is evident that the absence of thyroid secretion in the case of thyroidectomy produces marked disturbances in the growth of bony

tissue because under such condition the animal is unable to assimilate calcium. Parhon Marie (Endocrinology) while working on the calcium content of blood found that the blocd of thyroidectomized sheep (six weeks old at time of operation) a year after the operation had a lower percentage of calcium than the blood of the normal controls. Her experiments showed the following results:-

NORMAL ANIMAL	THYROIDECTOMIZED ANIMAL
1 kg, of fresh blood contains about 0.07gm, Ca	1 kg, of fresh blood contains about 0.053gm, Ca
1 kg, of dried blood contains about 0.36gm, Ca	1 kg, of dried blood contains about 0.27gm, Ca

The insufficient amount of calcium in the blood of thyroidectomized animals explains in part the tendency to hemorrhage in the case of insufficient thyroid secretion. Such disorders as urticaria, pruritis, and eczema are also attributed to insufficient calcium in the blood as result of hypothyroidism.

IX. TRANSPLANTATION EXPERIMENTS

A large number of experiments have been done on this field, using different methods and many kinds of animals. Results - in some cases there has been rapid degeneration and loss loss of the grafted organ, while in others the tissue has remained alive for a few months.

Different types of thyroid transplantation:-

1. HETEROPLASTIC TRANSPLANTATION

Heteroplastic transplantation is that in which the gland from one animal is grafted to various parts of the same animal. This type is always unsuccessful.

2. HOMOPLASTIC TRANSPLANTATION

Homoplastic transplantation is that in which the thyroid from one animal is grafted into another of the same species. This type is sometimes successful.

3. AUTOPLASTIC TRANSPLANTATION

Autoplastic transplantation is that in which a piece of thyroid is grafted to various parts of the same animal. This type is likely to be successful.

4. SYNGENESIOPLASTIC TRANSPLANTATION

Syngenesioplastic transplantation is transplantation into nearly related individuals. Results are intermediate between those obtained by auto and homoplastic transplantation. The transplanted gland lives for a certain time but it finally becomes absorbed by lymphocytal infiltration.

An interesting and successful case of thyroid transplantation was that performed on Mary Zembok (19 yrs, of age, of Joliet Ill.,).

* Mary had been a mentally defective child since birth.

* Glands in Health and Disease by Harrow B, 1922.

The mother had five children besides Mary, all of whom were normal. When Mary was two years old it became apparent that she would not develop into a normal child, so her mother confined her to the basement of their home, where she lived in darkness until Oct, 1920, (two months before the operation), when the health authorities learned of the case, and immediately removed the child to the hospital. The hospital authorities examined her and decided that the only hope for full recovery would be a gland transplantation. So the following December the operation was performed (the gland from a full-grown monkey was transplanted into the neck of the child). Result - after recovery from the operation Mary became a normal child, that is, both mental and physical development were restored.

X. INTERACTION OF THE THYROID WITH OTHER ORGANS

1. Relation of the Thyroid with Sexual Organs

* That there exists some relation between the thyroid and the reproductive organs is evident from the fact that in young thyroidectomized animals the sex gland are imperfectly developed, the resulting condition being sexual infantilism. Alquier and Theuveny working with adult animals (dogs) found a diminished activity in so far as production of spermatozoa was concerned, but no distinct change in the ovary.

*,An Introduction to the Study of the Endocrine Glands and Internal Secretions by Schäfer, E,.

2. Relation of Thyroid to Parathyroid

Experiments show that in thyroidectomized animals after thyroidectomy the parathyroid develops vesicles like the thyroid. Observers have noted that as result of removal of the thyroid there is hypertrophy of the parathyroids. But there is no sufficient evidence to support these facts.

3. Relation of the Thyroid with the Thymus

* There is no definite evidence of any important relation between the thymus and the thyroid. The thymus is usually enlarged or persistent in many conditions in which the thyroid is involved, as for example, simple goiter, myxedema, Graves' disease.

Asher and Ruchti found no change in the respiratory exchange after thyroidectomy in rabbits whether performed before or after thyroidectomy. Gudernatsch thought that thymus feeding inhibited to some extent the action of the thyroid feeding on tadpoles. Baumann found that foods enriched by the addition of protein-free nucleic acids of any origin stimulated growth in tadpoles. That there is an important indirect relation between the thyroid and the thymus through the sex glands and suprarenals is certain since each of these gland is closely associated functionally with the sex and parasex tissue, and both the thyroid and thymus are usually affected in conditions involving the suprarenals or sex-glands, as for example, Addison's disease, status lymphaticus, castration, and Graves' disease.

* Physiological Reviews Vol, II, 1922.

4. Relation of the Thyroid with the Pituitary

Rogowitsch and others working with rabbits have found that in 400% of the cases as result of thyroidectomy there was a marked enlargement of the anterior lobe and especially the pars intermedia of the pituitary body.*"They interpreted this enlargement as indicating that the pituitary could function vicariously for the thyroid." Simpson and Hunter repeated the work of Rogowitsch and his companions but did not confirm exactly the same results. They found that in rabbits there is slight hypertrophy of the anterior lobe, but this was rarely more than 15 - 20% after 5 or 6 months.

Many investigators have found traces of iodin in both human and sheep pituitary while others have failed. Simpson and Hunter showed conclusively that the sheep pituitary contained no iodin even in animals recently fed with this element.

Livingston experimenting with rabbits found that feeding of dried thyroid protects male thyroidectomized rabbits against pituitary hypertrophy. No pituitary hypertrophy was observed in thyroidectomized female rabbits even without thyroid feeding.

Hewitt experimenting with white rats reported that thyroid feeding in white rats caused pituitary enlargement.

The idea that the pituitary and thyroid were functionally related was suggested by Virchow and was based on the morphological resemblance of the colloid filled follicles of the pars intermedia to the thyroid follicle. (Physiological Reviews).

*Marine D. Physiological Reviews Vol, II, 1922., Page 538.

5. Relation of the thyroid with the Suprarenal

Marine and Baumann experimenting with rabbits found in 80% of the cases that when the suprarenal cortex was injured either by freezing or by partial removal there was a marked chronic increase in heat production. The increase began within three to six days after the suprarenal injury and lasted from two weeks to several months. Heat production was increased up to 60% or more above normal. They also found that if the thyroid gland was removed and the metabolism allowed to fall to the myxedema level prior to the injury of the suprarenal cortex, the increase in heat production did not occur. Scott has repeated this experiment using cats and has confirmed these findings of Marine and Baumann.

In 1899 Golyakowski ligated the suprarenal vessel of dogs - result - there was an increased carbon dioxide output. There is some evidence that the increased heat production is associated with a loss of iodin from the thyroid and recently Black, Hupper, and Rogers, have published evidence that feeding suprarenal gland residue to dogs increased the iodin store of the thyroid gland. This reaction with increased heat production appears to be a suprarenal cortex thyroid interrelationship. "Our present interpretation is that the suprarenal cortex exercises a regulatory or inhibitory control over thyroid activity and when this is withdrawn the thyroid automatically responds with increased function. It may be well to state at this point that there is evidence that the suprarenal cortex exercises an inhibitory control over other tissue functions as well. The thyroid suprarenal interrelation, therefore, is not an isolated one. The

Physiological Reviews Vol. II, 1922. Page 536.

practical application of these observations may be of great importance; for example the enlargement of the thyroid at puberty, during menstruation, pregnancy and menopause may be thus partly explained. The effect of bacterial toxins in causing thyroid hyperplasia may be in part determined by a primary injury to the suprarenal cortex. Other well known facts involving obvious interrelations as, fo example, the hypersusceptibility of certain individuals to dessicated thyroid and thyroxin, probably have as their basis this fundamental thyroid suprarenal cortex interrelationship.

Finally the normal involution of the suprarenal cortex in infants should be mentioned here. The destruction of the reticular and fascicular zones of the cortex has been observed only in infants and begins during the second or third week of extra-uterine life. The process starts as a hemorrhagic infiltration of the two inner zones and goes on to necrosis, destruction and absorption of these layers with collapse and folding of the glomerular zone on to the medulla. The duration of the stages of absorption and healing is indefinite. Some authors estimate it at two or three weeks and others at two or three months. The end result, however, of this destruction is a marked decrease in the volume cortex so that a child one year old has a smaller total volume of cortex than at birth.

The physiological significance of this rapidly progressive partial destruction of the cortex is unknown. It is not accidental or traumatic. Its occurrence in accessory suprarenals as well suggests that it is a systemic purposeful reaction to meet the altered conditions incident to extra-uterine life. In the light of the re-

lation of experimental injury of the suprarenal cortex in rabbits, dogs, and cats to increased heat production, it is suggested that one of the effects of the cortical destruction in infants may be increased heat production through thyroid activation."

6. Relation of the Thyroid with the Liver

Krause and Cramer found that in cats and rats fed with thyroid, glycogen disappeared from the liver; but there was no glycosuria as the sugar had been conveyed to the tissues and become oxidized. Parhon repeated same experiments with rabbits, and obtained same results as Krause and Cramer.

7. Relation of Thyroid with the Pancreas

Thyroid secretion seems to have an antagonistic effect on pancreatic secretion. Experiments show that after removal of the pancreas the animal in question exhibits glycosuria. Removal of the thyroid caused glycosuria to disappear.

The tendency to glycosuria in Graves disease is believed to be probably due to the inhibition of pancreatic secretion by the thyroid.

XI. DISEASE OF THE THYROID

1. Cretinism

Cretinism is a disease due to atrophy of the thyroid gland. It occurs in children, and the symptoms are similar to those obtain-

ed as result of thyroidectomy.

a). Symptoms:-

1. Arrested growth
2. Head and face deformed
3. Idiotic expression
4. Face pale
5. Hair very thin
6. Skin dry
7. Abdomen swollen
8. Development of generative organs delayed

b). Cure:-

Extracts of thyroid given with food or injected either subcutaneously or intravenuosly.

2. Myxedema

Myxedema is a disease due to atrophy of the thyroid, it occurs in adults and produces similar conditions to those described in the child. The disease is called myxedema to differentiate it from cretinism which is characteristic of children and also *"to denote the mucous fluid that gathers beneath the tissue and that gives rise to swellings all over the body."

a). Cause of disease:-

Probably due to the presence of an excess of mucin a substance that gives the ropy consistency to saliva.

b). Symptoms:-

The subject becomes deformed in appearance, has a dull mind,

* Glands in Health and Disease by Harrow B, Page 23.

sluggish movements, unsteady gait, and poor appetite.

c). Cure:-

Administration of thyroid extract. This to be efficient must be at regular intervals and kept up indefinitely to prevent relapse.

3. Endemic Goiter

In this disease the front of the neck becomes swollen due to enlargement of the gland. The enlargement is due to a deficient secretion of the gland rather than to an excess secretion as would be expected by the fact that the neck becomes swollen. That it is due to hyposecretion is confirmed by the fact that it is cured by treating the patient with thyroid extracts. Long before iodine was found to be an essential constituent of the gland the disease was cured by applying poultices of burned sea-weed and by painting iodine on the neck.

4. Exophthalmic Goiter

This disease is due to excessive thyroid secretion. It is characterized by four symptoms:-

a). Hypertrophy of the thyroid

b). Exophthalmos

c). Tachycardia

d). Nervous excitability

The disease progresses slowly as the organism becomes flooded with the excessive secretion. First symptom - nervousness accompanied by conjestion and swellings of the neck after fatigue. Other symptoms which follow are:-

a). Eye ball protruded

b). Strong emotion plus violent palpitation

c). Sleep not sound

d). Rapid pulse from 90-120 beats/minute. By violent emotion or fatigue the pulse rate may rise as high as 100 -150 or even as high as 180.

e). Examination of the heart shows that the right ventricle is usually hypertrophied and dilated.

f). Intercellular oxidation is accelerated and accompanied by an increased expenditure of energy.

g). The respiratory interchange of gases shows an increase of 50% and the intake of oxygen from 70-80%.

h). There is more heat given off due to increased respiration.

i). The alimentary canal shows morbid congestion and irritability.

j). There is some hypertrophy of the liver, spleen, and lymph.

k). The metabolism of albumin is increased, and of carbohydrates decreased. But there is no change in the metabolism of minerals.

l). In the blood there is an increase in the number of mononuclear leucocytes and eosinophile cells.

m). Sexual disturbances - men usually lose their sexual appetite. In women mestruation becomes irregular, may cease to appear totally and reappear with the improvement of the disease.

This disease occurs in people predisposed to nervous instability and supersensitiveness.

In autopsy the gland is found very large, especially the right lobe, the veins are dilated and gorged with blood; the gland

is soft and sort of brownish red in color. The colloid material is softer, paler, and contains less chromophile than normally.

Treatment of the disease:-

By operative surgery which consists in reduction of the volume of the gland. Reduction in volume brings about a decrease in the normal vascularization and reduces its secretory activity. Treatment is very successful. In the case where the thymus is enlarged surgery cannot be practiced, so in such cases X-ray application reduces the function.

XII. SUMMARY

It was once assumed that the function of the thyroid was to destroy the toxic substances circulating in the blood, but this is no longer believed. At present it is thought that the function of the gland is to produce an internal secretion which is essential to maintain the body in a healthy condition.

Our modern knowedge of the function of the thyroid has been obtained as result of experiments performed on different animals.

The fact that extracts of thyroid tissue or iodothyrin when absorbed into the blood remove the evil effects resulting from loss of function of the thyroid seems to prove that the normal function of the gland is not merely to excrete poisonous material from the blood, but it suggests that the thyroid tissue normally gives off to the blood a substance which in some way , not yet definitely understood, favorably affects the nutrition of all parts of the tissues of the body.

The secretion of the active principle or principles is

is probably under the control of the sympathetic. Whether the influence of the active material is direct on the tissues themselves, or indirect through the nervous system, is still doubtful. The thyroid is not equally important on all groups of animals. Adult herbivora can live in good health without a thyroid, while the carnivora under such conditions will frequently suffer severely and die.

The thyroid secretion seems to antagonize an unknown toxic substance which is present in the body in the course of normal metabolism. When the gland is removed as in the case of thyroidectomy or degeneration of the gland this toxic substance, is imperfectly excreted, therefore it accumulates in the tissues gets in the circulation by means of the blood-stream and produces the fatal symptoms of thyroidectomy by a process of auto-intoxication.

BIBLIOGRAPHY

Allen, B. M. — The result of thyroid removal in larvae of Rana pipiens. Jour, Exper, Zool, Vol, 24, 1928. Philadelphia.

Bailey-Miller. — Text-book of Embryology (2nd, Edi.) Wm, Wood and Co., MDCCXI.

Beddard, A. P. — Recent advances in physiology and Biochemistry Longmans Green and Co., 1906.

Bohm, A.A. & Von-Davidoff, — Text-book of Histology (2nd, Edi.,) Wm, B, Saunders and Co., 1904.

Brown, W.L. — The Biology of the Endocrine System Med, Jour, Apr, 5, 1922. N.Y.

Brubaker, A.P. — Text-book of Human Physiology (7th, Edi,) Blakiston's Son and Co, Copyright 1922.

Chandra, C. — Endocrine Glands Omin and Co, 1923.

Cunningham, J.I. — Hormones and Heredity Constable and Co, 1921.

Dale, H.H. — The Physiology of the thyroid Practitioner London 1915.

Dercum, F.X. — The Biology of Internal Secretion
W.B. Saunders Co, 1924.

Dott, M.M. — An investigation into the function of the pituitary and thyroid glands.
Quart, Jour, Exper, Physiol, Vol, 13.
London 1923.

Faught and Ryan — Function and Interelations of the Endocrine Glands.
Am, Jour, Of Med, Sci, 1928

Gley, E. — The Internal Secretions
(Their physiology and application to pathology), Trans, from the Fr, and edited by M, Fishberg
Paul B, Hoeber 1917.

Gray, — Anatomy of the Human Body (21st, Edi.)
Lea and Febiger 1924.

Harrow, B, — Glands in Health and Disease
E.P. Dutton and Co, (Copyright 1922).

Herring, P.T. — The action of the thyroid upon the growth of the body and organs of the white rat.
Quart, Jour, Exper, Physiol,
Vol, II, London 1917.

Hoskins, E.R. — Endocrinology Vol, 4, 1920.

" " " — Jour, Exper, Zool, Vol, 11, 1916.

" & Hoskins — Interelation of the thyroid and hypophysis in growth and development of Frog larvae. Endocrinology 1920, Los Angeles.

Hoskins, M.M. — Regeneration and transplantation of the thyroid, Endocr, Vol, 7, 1923.

Howell, W.H. — Text-book of Physiology W.B. Saunders and Co, 1924.

Hunt, R. — Relation of Iodine to the Thyroid Gland Chicago 1907 (pamphlet).

Kendall, E.C. — The physiological action of the thyroid hormone. Am, Jour, of Physiol, Vol, 49, 1919 Baltimore

Kendall, E.C. — Isolation of the iodine compound which occurs in the thyroid (1st,paper) Jour, of Biol, Chem, Vol, 39, 1919. Baltimore (second paper) Vol, 40, 1919.

Lewis & Stöhr — Text - book of Histology (2nd, Edi,) P. Blakiston's Son and Co, (Copyright 1923).

Marine, D, — The present status of the function of the thyroid
Physiological Reviews, Vol, 2, 1922,
Baltimore

Parhon, M. — The calcium content of the blood of thyroidectomized animals
Endoc, Vol, 7, 1923.

Pende, N. — Endocrinologia, Patologia, e Clinica degli Organi e Secrezione Interna
Parte I, Milano 1920.
" II, " 1922.

Rowe, A, W, — The diagnosis and treatment of the thyroid diseases as controlled by the metabolic rate
Endocr, Vol, 7, 1923.

Schäfer, E.A. — Text-book of Physiology
Vol, 1, Macmillan Co, 1918.

Schäfer, E. — An introduction to the study of the endocrine glands and internal secretions
Lane Medical Lectures 1923
Published by Stanford University, Cal,1914.

Vincent, S. — Internal Secretion and the Ductless Glands. Physicians and Surgeons Bk,Co,
3rd, Edi, N.Y. 1925.
2nd, " " " 1922.

NOTE:-

All articles and books on this bibliography have been read completely or in part in so far as they relate to the subject of the physiology of the thyroid gland.

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